REMARKS

Prior to entry of this Amendment, Claims 9-16 were pending and under consideration. No claims being are cancelled, added or amended. Thus, Claims 9-16 are still pending and under consideration.

The Amendments of the Specification

A typographical error in the specification has been corrected. The amendment does not add new matter.

Rejection of Claims 9-16 under 35 U.S.C. §103(a)

[Note that the various rejections are not addressed in the same order as presented in the final Office Action mailed July 8, 2003.]

Claims 9-16 stand rejected under 35 U.S.C. §103(a) as being allegedly unpatentably obvious over Drmanac *et al.* (U.S. Patent No. 6,383,742) in view of Kagawa *et al.* (WO 98/08975). The rejection traversed as applied to Claims 9-16 on the ground that the Patent Office has failed to establish a *prima facie* case of obviousness.

In rejecting claims under §103(a), the Patent Office bears the burden of establishing a *prima facie* case of obviousness (MPEP § 2142). To establish a *prima facie* case, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the references or to combine their teachings. Second, there must be a reasonable expectation of success. Third, the prior art reference(s) must teach or suggest each and every limitation of the rejected claims. The teaching or suggestion to make the claimed combination *and* the reasonable expectation of success must *both* be found in the prior art, and *not* in Applicants' disclosure. *In re Vaeck*, 20 USPQ2d 1438 (Fed. Cir. 1991); MPEP §2142.

At a minimum, the references cited by the Patent Office, whether taken alone or in combination, fail to teach or suggest each and every limitation of the rejected claims.

Pending Claim 9 recites a method of detecting a target sequence in a sample comprising the following steps: (a) providing a substrate comprising an array of capture probes coated with a recombinase; (b) contacting said target sequence with said array, to form an assay complex; and (c) detecting said assay complex to detect said target sequence in said sample.

Drmanac *et al.* teach a method of detecting a target nucleic acid including the steps of providing an array of probes affixed to a substrate and hybridizing a target nucleic acid to the array. The Patent Office admits that Drmanac *et al.* do not teach that their arrayed of capture probes are coated with recA. Rather, the Patent Office alleges that Drmanac *et al.* (at Column 9 lines 22-26) "clearly" suggests that recA is present on the array. Applicants disagree.

The Patent Office interprets the parenthetical phrase "(especially where a recA protein is present to permit hybridization under non-denaturation conditions)" (Column 9 lines 24-26) as suggesting that the array of capture probes are coated with recA. In making this interpretation, the Patent Office has ignored the later teaching in Drmanac *et al.* that recA is used to treat the *target nucleic acid* (Column 12 lines 61-64): "A nucleic acid sample to be sequenced may be fragmented or otherwise treated (for example, by the use of recA) to avoid hindrance to hybridization from secondary structure in the sample." Drmanac *et al.* includes extensive description of the preparation of DNA arrays (see, e.g., column 24, Example 8), but *no mention* of coating such arrays with recombinase. Thus, contrary to the allegation by the Patent Office, Drmanac *et al.* do not suggest, "clearly" or otherwise, an array of capture probes coated with recA.

Thus, there is no teaching or suggestion of providing a substrate comprising an array of capture probes coated with a recombinase, or of using such an array in the methods as claimed.

The Kagawa *et al.* reference does not remedy the deficiencies of Drmanac *et al.* Kagawa *et al.* teach a method for targeting, enriching, detecting and/or isolating a double stranded nucleic acid target sequence in a sample. The method includes the steps of (a) providing at least one type of recombinase, at least one type of homologous probe, and at least one type of heterologous probe, and (b) mixing the recombinase, the homologous

probe, and the heterologous probe with the double-stranded nucleic acid target sequence in the sample. These steps are carried out in solution. In some embodiments, the reaction mixture is subsequently contacted with a solid support designed to selectively bind the complex of the double stranded nucleic acid target sequence and the homologous probe. In Kagawa *et al.*, there is no teaching or suggestion of providing a substrate comprising an array of capture probes coated with a recombinase, or of using such an array in the methods as claimed.

Therefore, Drmanac *et al.* and Kagawa *et al.*, either alone or in combination, do not teach or suggest the limitation of providing an array of capture probes coated with a recombinase. In addition, these references alone or in combination do not teach or suggest the subsequent step of contacting a recombinase-coated array with target sequences to form a complex with target sequences. These deficiencies are fatal to the rejection.

For the reasons discussed above, Applicants submit that the combination of Drmanac *et al.* in view of Kagawa *et al.* fails to render Claim 9 *prima facie* obvious. Specifically, the cited combination of references does not teach each and every limitation of the rejected claims. All other claims to which the rejection appears germane depend from Claim 9. Accordingly, *prima facie* obviousness is not established and the rejection of Claims 9-16 under 35 U.S.C. § 103(a) should be withdrawn.

Rejection of Claims 9-14 under 35 U.S.C. §103(a)

Claims 9-14 stand rejected under 35 U.S.C. §103(a) as being allegedly unpatentably obvious over Radding *et al.* (U.S. Patent No. 4,888,274) in view of Drmanac *et al.* (U.S. Patent No. 6,383,742). The rejection is traversed as applied to Claims 9-14 on the ground that the Patent Office has failed to establish a *prima facie* case of obviousness.

In rejecting claims under §103(a), the Patent Office bears the burden of establishing a *prima facie* case of obviousness as indicated above. At a minimum, the references cited by the Patent Office, whether taken alone or in combination, fail to teach or suggest each and every limitation of the rejected claims.

Radding *et al.* teach a method of detecting a target duplex DNA that involves contacting a target DNA with solution-phase biotinylated capture probes that are coated

with a recombinase to form a stable probe/target complex. Following contact, the bound probe/target complex is captured by use of avidin or strepavidin. Radding *et al.* do not teach or suggest providing an array of capture probes coated with a recombinase.

The teachings of Drmanac *et al.* were discussed above.

Neither Radding *et al.* nor Drmanac *et al.*, alone or in combination, do not teach or suggest the limitation of providing an array of capture probes coated with a recombinase. In addition, these references alone or in combination do not teach or suggest the subsequent step of contacting a recombinase-coated array with target sequences to form a complex with target sequences. These deficiencies are fatal to the rejection.

For the reasons discussed above, Applicants submit that the combination of Radding *et al.* in view of Drmanac *et al.* fails to render Claim 9 *prima facie* obvious. Specifically, the cited combination of references does not teach each and every limitation of the rejected claims. All other claims to which the rejection appears germane depend from Claim 9. Accordingly, *prima facie* obviousness is not established and the rejection of Claims 9-14 under 35 U.S.C. § 103(a) should be withdrawn.

Rejection of Claims 9-16 under 35 U.S.C. §103(a)

Claims 9-16 stand rejected under 35 U.S.C. §103(a) as being allegedly unpatentably obvious over Kagawa *et al.* (WO 98/08975) in view of Drmanac *et al.* (U.S. Patent No. 6,383,742). The rejection traversed as applied to Claims 9-16 on the ground that the Patent Office has failed to establish a *prima facie* case of obviousness. At a minimum, the references cited by the Patent Office, whether taken alone or in combination, fail to teach or suggest each and every limitation of the rejected claims, as discussed above.

The Kigawa *et al.* and the Drmanac *et al.* references were discussed above. The Kigawa *et al.* reference and the Drmanac *et al.* reference, individually or in combination, fail to teach or suggest the step of providing a substrate comprising an array of capture probes coated with a recombinase, and fail to teach or suggest the step of contacting target sequences with such an array to form an assay complex.

Assuming, *arguendo*, one of ordinary skill decided to modify the array of Drmanac *et al.* by immobilizing recombinase-coated capture probes of Kigawa *et al.* in an array, the

rejection would still fail. To establish *prima facie* obviousness, the Patent Office also bears the burden of showing that one of skill in the art would have been motivated to make the modification or combine the teachings of the references. The Patent Office alleges that one would have been so motivated "for the obvious benefit of economy of reusable components." However, this is unsupported speculation. It is not known whether a *recombinase*-coated array would be reusable.

The Patent Office also alleges that it would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to modify the method of Kigawa *et al.* "by immobilizing their capture probes onto the support prior to contact with the target sequence." As indicated above, the method of Kigawa *et al.* includes the steps of (a) providing at least one type of recombinase, at least one type of homologous probe, and at least one type of heterologous probe, and (b) mixing the recombinase, the homologous probe, and the heterologous probe with the double-stranded nucleic acid target sequence in the sample in a solution phase. In certain embodiments, the homologous probe is biotinylated and subsequently immobilized. The homologous capture probes of Kagawa *et al.* are therefore *always* present in association with heterologous probes. Assuming for the sake or argument that one of ordinary skill decided to modify the array of Drmanac *et al.* to use the probes of Kigawa *et al.*, the heterologous probes would also have to be included in association with the homologous probes, although these heterologous probes would not be attached to the surface of the array. There is no reasonable expectation of success that such a combination would be operable. For example, in such an array, the presence of the heterologous probes might interfere with binding of target sequences.

According to the Patent Office (page 7 of the Office Action mailed 8 July 2003), where process steps are known, absent unexpected results, the rearrangement of the process steps is *prima facie* obvious (citing *In re Burhans* 154, F.2d 690, 69 USPQ 330 (CCPA 1946)).

The Patent Office's reliance on *Burhans* is misplaced. In *Burhans*, the application included claims to a method of preventing rancidity of flour through the use of carbon dioxide. The method consisted of the following steps:

a. separating the germs from the wheat kernels and the manufacture of flour from the rest of the kernels;

b. aging the germless flour;

c. incorporating in the aged germless flour finely divided non-rancid wheat germ constituents; and

d. impregnating the flour with carbon dioxide.

The court determined, based on consideration of the disclosure in five issued patents, that each of the claimed process steps was in fact *old in the art* and held that the methods defined in the appealed claims were not patentable over the art of record absent proof that the order of performing these known steps produced new and unexpected results.

In contrast to the process steps of the claims in *Burhans*, the present Claim 9 is *not* a mere arrangement of *known* process steps. Specifically, none of the references cited by the Patent Office include a step of providing a substrate comprising an array of capture probes coated with a recombinase. Additionally, none of the cited references include a step of contacting a target sequence with such an array to form an assay complex, and none of the references include a step of detecting the assay complex.

For the reasons discussed above, Applicants submit that the combination of Kagawa *et al.* in view of Drmanac *et al.* fails to render Claim 9 *prima facie* obvious. All other claims to which the rejection appears germane depend from Claim 9. Specifically, the cited combination of references does not teach each and every limitation of the rejected claims. The cited combination of references do not provide motivation to modify the references or to combine their teachings. Accordingly, *prima facie* obviousness is not established and the rejection of Claims 9-16 under 35 U.S.C. § 103(a) should be withdrawn.

Conclusion

Applicants submit that Claims 9-16 satisfy all of the statutory requirements for patentability and are in condition for allowance. An early notification of the same is therefore kindly solicited. No fees beyond the fee under 37 C.F.R. §1.17(e) being submitted concurrently herewith are believed due in connection with this Amendment. However, the Commissioner is hereby authorized to charge any additional required fees, or credit any overpayment, to Dorsey & Whitney LLP Deposit Account No. 50-2319 (Order A-68767-1/AMP/JFB (470193-32)).

Respectfully submitted,

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